# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 207318Orig1s000

# OFFICE DIRECTOR MEMO

**Deputy Office Director Decisional Memo**

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| **Date** | (electronic stamp) |
| **From** | Robert Temple, MD |
| **Subject** | Deputy Division Director Summary Review |
| **NDA/BLA #** | 207318 |
| **Applicant Name** | Acadia Pharmaceuticals, Inc. |
| **Date of Submission** | September 1, 2015 |
| **PDUFA Goal Date** | March 29, 2016 |
| **Proprietary Name / Established (USAN) Name** | May 1, 2016 |
| **Dosage Forms / Strength** | Nuplazid/pimavanserin |
| **Proposed Indication(s)** | Tablet, coated, 17 mg |
| **Action/Recommended Action for NME:** | Hallucinations and Delusions Associated with Parkinson's Disease |

| **Material Reviewed/Consulted** OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Medical Officer Review | Paul Andreason, MD |
| Statistical Review | Eiji Ishida, MS<br>Peiling Yang, Ph.D.<br>H.M. James Hung, Ph.D. |
| Pharmacology Toxicology Review Supervisory | Amy M. Avila, PhD<br>Aisar Atrakchi, PhD |
| CMC Review/OBP Review Application Technical Lead | David Claffey, PhD |
| Clinical Pharmacology Review | Kofi Kumi, PhD<br>Di Zhou, PhD<br>Kevin Krudys, PhD<br>Hao Zhu, PhD |
| OPDP | Susannah O'Donnell, MPD |
| OSI | Cara Alfaro |
| OSE/DMEPA | Loretta Holmes, PharmD |
| **Other** | |
| Pediatrics and Maternal Health | Amy Taylor, MD |
| CSS | Martin Rusinowitz, M.D.<br>Jovita Randal-Thompson, Ph.D. |
| QT-IRT | Li Zhang |

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
OPQ=Office of Pharmaceutical Quality

I. Benefit Risk Summary and Assessment

There is disagreement within the division as to whether the benefits of pimavanserin in treating hallucinations and delusions in patients with Parkinson's Disease Psychosis (PDP) which all agree have been demonstrated, outweigh the risks of an anti-psychotic (risks reasonably well-established in patients with dementia-associated psychosis) in a relatively frail elderly population with PDP. Evidence of risk in the PD population studied with pimavanserin is not easy to assess, as will be discussed further below, because there is no consistent specific finding; i.e., the deaths (4 total; 3 pimavanserin, 1 placebo) and other serious adverse events have no apparent mechanistic relationship, unlike virtually all serious drug toxicities. That noted, the consistent finding of increased mortality in dementia-associated psychosis shows a fairly similar pattern, with a wide range of causes of mortality. Dr. Andreason (CDTL and primary reviewer) finds only modest benefit of pimavanserin and considers it outweighed by the risk; Dr. Mathis (Division Director) finds the benefit stronger and clinically meaningful when properly assessed by examining individual responses, and notes the absence of any FDA approved treatment for PDP. He also notes the hope that pimavanserin, which does not have dopamine-blocking activity, would not worsen PD motor symptoms was assessed in the controlled trial. Pimavanserin did not in fact worsen PD symptoms. I agree with Dr. Mathis's conclusion. In brief, all recognize PDP as an important problem, occurring in perhaps 40-50% of patients with PD, and with no approved treatment. The mean effect of pimavanserin on the 9-item (0-5 on each item) assessment scale, the Assessment of Positive Symptoms-Parkinson's Disease (SAPS-PD) used in the supportive study was a mean reduction compared to placebo, of 3 points on a scale that goes from 0-45. The mean effect may indeed be modest, a 3 point reduction compared to placebo from a starting value of about 15-16 points, but some patients had much larger effects, e.g., 10 points or more, and some had complete resolution of symptoms. These responses cannot be regarded as modest. As noted by Dr. Mathis, and also discussed further below, the serious adverse events were more common on drug (16/202, 7.9%) than placebo (8/231, 35%), but they had no unifying pattern and are hard to interpret as drug related, despite the numerical difference.

| Dimension | Evidence & Uncertainties | Conclusions & Reasons |
|---|---|---|
| **Analysis of Condition** | Hallucinations and delusions in Parkinson's disease are disturbing and can be disabling. They can lead to diminished interactions with family and friends and can lead to nursing home placement. | Safe and effective treatment of PD hallucinations and delusions would be relevant to a large population with a distressing and debilitating condition. |
| **Current Treatment Options** | There is no FDA approved treatment for Parkinson's Disease Psychosis (PDP). Published controlled studies report effectiveness of clozapine. Available antipsychotics have dopamine blocking properties that can worsen motor function in PD. | No approved FDA reviewed treatment for PDP. Clozapine, used off label, requires frequent neutrophil monitoring because of the risk of severe neutropenia and is difficult to use. |
| **Benefit** | A 34 mg daily dose of pimavanserin provides a statistically significant 3 point reduction in the primary endpoint (SAPS-PD score), with larger responses in some patients. Both the hallucination and delusion components were improved. | Effectiveness was established by a single statistically strong ($p = 0.0014$) study, with effects seen on both hallucinations and delusions. |
| **Risk** | Serious AEs (SAEs) were seen in 16/202 (7.9%) patients on 34 mg of pimavanserin in all controlled trials vs 8/231 on placebo; there were 3 deaths on pimavanserin vs 1 on placebo. No single SAE appeared more than once or twice. | Pimavanserin appears to have increased numbers of SAEs and perhaps mortality similar to what is seen with other antipsychotics when they are used in demented elderly patients. It is noteworthy that in its controlled trial, pimavanserin did not worsen symptoms of PD. |
| **Risk Management** | Whether the SAEs and mortality findings are real is uncertain in the absence of a mechanistic relationship. Labeling will include the standard box warning for antipsychotics concerning use in patients with dementia-related psychosis, but as Dr. Mathis notes, absent a mechanism there is no good way to monitor and prevent them. | The box warning will allow a candid discussion of benefits and potential risks.<br><br>There is also a warning about avoiding use of pimavanserin with other drugs that prolong the QT interval. |

II. Background

As explained fully by Drs. Mathis and Andreason, psychosis associated with PD (PDP), whether it is a part of the underlying disease or is a response to dopamine replacement or dopamine enhancing treatments for PD, is common in PD and is very troubling in a patient population whose ability to function and interact with others is already limited. PDP is sometimes treated by lowering the dopamine replacement or dopamine-enhancing drugs but at a cost in the effectiveness of PD treatment of motor symptoms. There is no approved PDP treatment, although as Drs. Mathis and Andreason note, clozapine has been effective in controlled trials and both it and quetiapine are used, albeit with little controlled trial support for quetiapine. Both drugs would be expected, because of their anti-dopamine effects, to worsen the state of motor function (as would lowering the doses of the L-DOPA and dopamine agonists used to treat PD, an unattractive treatment option for PDP).

Pimavanserin was shown in its controlled study to reduce the hallucinations and delusions that are prominent features of PDP and it was also shown not to exacerbate the motor symptoms of PD, an important property, as measured by a lack of effect on the UPDRS Parts II and III (Unified Parkinson's Disease Rating Scale Parts II and III).

It is well-recognized, and noted in labeling of all anti-psychotics, that anti-psychotics, when used in patients with dementia-related psychosis, a generally fragile population, increase the rates of deaths from various causes and of other serious adverse effects (although this is not always seen, e.g., in the CATIE study of atypical anti-psychotics in patients with Alzheimer's Disease NEJM 2006; 355: 1525-38). Because of this, none of the anti-psychotics are approved for this use, although they are used off-label. It was uncertain at the outset whether pimavanserin would have similar properties in the PD population, also a fragile population, but perhaps less fragile than the dementia population.

Initial controlled trials (012, 014) studied a range of doses of pimavanserin (8.5 mg to 34 mg) and used the full Schedule for the Assessment of Positive Symptoms (SAPS-H & D) of schizophrenia, a 20-item scale including assessments of delusions, hallucinations, abnormalities in language and behavior, and disordered thought processes. Study 014 compared doses of 8.5 mg and 17 mg to placebo in a 6-week randomized study. It was to include 280 patients but was stopped after 123 were enrolled because of the negative results seen in Study 012, and the truncated study showed no significant treatment effects on SAPS. It is of interest, however, that there was a nominally statistically significant effect on the clinician rated global measure of improvement from baseline (CGI-I), p=0.023.

Study 012 compared 8.5 mg and 34 mg pimavanserin to placebo in a 6-week study in patients with PDP using the SAPS-H & D scale and several other endpoints including the motor function measure UPDRS, parts II and III. There were about 100 patients per treatment. Each treatment group was tested at a p of 0.025. The results showed no significant effect on the primary endpoint, but did show nominal significance on the SAPS-H (hallucinations) item and on the overall SAPS-H&D 20-item score in the US, as well as better results on the 34 mg dose than on 8.5 mg. It also showed no adverse effect on the UPDRS parts II and III. This led to planning of the 020 Study in North America and use of the SAPS-PD (9-item scale focused an hallucinations and delusions).

III. Effectiveness

The effectiveness of pimavanserin in PDP was supported by Study ACP-103-020 (hereafter Study 020), which is fully described in the Clinical Review (Andreason) and in the Statistical Review (Ishida, Yang, Hung). Study 020 was a 6-week placebo-controlled randomized trial comparing 34 mg/day of pimavanserin with placebo in 199 patients (94 placebo, 105 pimavanserin).

Patients > 40 years of age with at least one year of PD and at least one month of weekly psychotic symptoms, including visual hallucinations and/or auditory hallucinations, and/or delusions, could be entered if they had a severity of at least 4 on the hallucinations or delusions scales or a total of 6 on the Neuropsychiatric Inventory (NPI), and if their baseline SAPS-PD global hallucinations or delusions (items H7 or D13) scores were ≥ 3 with a score of at least 3 on another, non-global item. The above inclusions were enrichment features, i.e., ensuring sufficient symptomatology to allow a showing of improvement.

Patients were seen every 2 weeks and assessed for all primary and secondary endpoints except for UPDRS Parts II and III, which were assessed only at baseline and week 6. The primary endpoint was the SAPS-PD, with 9-items from the SAPS, each rated 0-5.

H1 – auditory hallucinations
H3 – voices conversing
H4 – somatic or tactile hallucinations
H6 – visual hallucinations
H7 – global rating of severity of hallucinations

D1 – persecuting delusions
D2 – delusions of jealousy
D7 – ideas and delusions of reference
D13 – global rating of severity of delusions

Ratings were carried out remotely by blinded raters using videoconference technology.

Secondary endpoints included:

GCI-S - clinician scale measuring current illness severity, rated from 1 (normal) to 7 (extremely ill).

CGI-I – clinician scale measuring change from baseline from 1 (very much improved) to 7 (very much worse).

UPDRS II & III (27 items from activities of daily living and motor examinating, range of 0 to 108.

CGI-S and CGI-I, assessed by study investigators blinded to SAPS-PD scores.

Primary endpoint results, and the hallucination and delusion components are shown in Table 1, taken from the labeling that will be approved.

**Table 1 Primary Efficacy Analysis Result based on SAPS-PD (N = 185)**

| Endpoint | Treatment Group | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | Placebo-subtracted Difference[a] (95% CI) |
|---|---|---|---|---|
| **SAPS-PD** | NUPLAZID | 15.9 (6.12) | -5.79 (0.66) | -3.06* (-4.91, -1.20) |
| | Placebo | 14.7 (5.55) | -2.73 (0.67) | -- |
| SAPS-PD Hallucinations[b] | NUPLAZID | 11.1 (4.58) | -3.81 (0.46) | -2.01 (-3.29, -0.72) |
| | Placebo | 10.0 (3.80) | -1.80 (0.46) | -- |
| SAPS-PD Delusions[b] | NUPLAZID | 4.8 (3.59) | -1.95 (0.32) | -0.94 (-1.83, -0.04) |
| | Placebo | 4.8 (3.82) | -1.01 (0.32) | -- |

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

[a] Difference (drug minus placebo) in least-squares mean change from baseline.

[b] Supportive analysis.

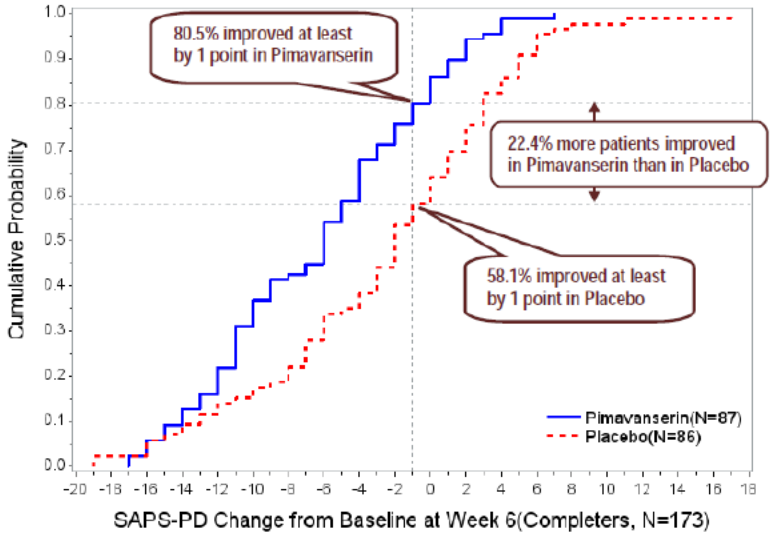
* Statistically significantly superior to placebo.

The SAPS-PD hallucination and delusion components were not planned primary or sequential secondary endpoints (so no p-values are given) but it is helpful to see that both components were affected. Although they were not primary or planned secondary endpoints, they were nominally strongly significant, as noted in Dr. Andreason's review (p 52, Table 7), effects on CGI-I and CGI-S, as well as on exploratory endpoints like caregiver burden.

Dr. Andreason concluded that the effect on the primary endpoint (SAPS-PD) of about 3 points, as well as the approximately 23% improvement in CGI represented "minimal" improvement that did not outweigh his safety concerns. I believe it is critical to look, not just at mean results, but at the distribution of responses as well as for virtually all drug treatments there are greater and lesser responses. We are increasingly able to predict those by genetic/proteomic testing but for most symptomatic conditions we will not have such clear explanations. Nonetheless, the distribution of responses shown in cumulative distribution curves (fig 1) or in bar graphs (fig 2) is informative.

Fig 1, taken from the statistical review shows that, for example, 81% of patients on pimavanserin and 58% of patients on placebo improved by at least one point at week 6. Perhaps of greater interest, about 34% on pimavanserin vs 17% on placebo improved by 10 points.

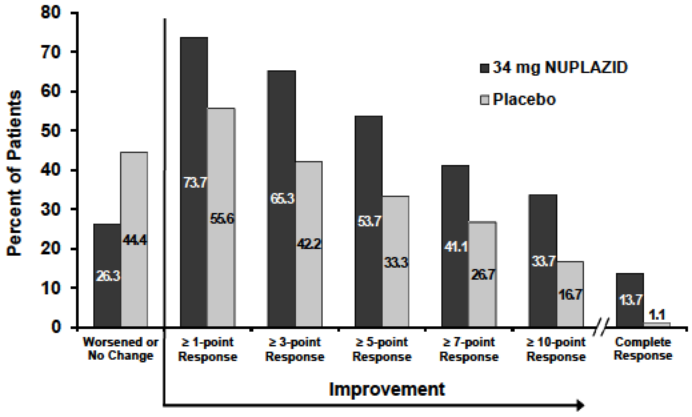
**Fig 1: Cumulative Distribution Function by Treatment at Week 6 for Completers (N=173)**




Note: A patient improves if the change from baseline score to Week 6 is less than 0.
Source: Reviewer's analysis

The same data can be shown as bar graphs, showing rates of specific responses.

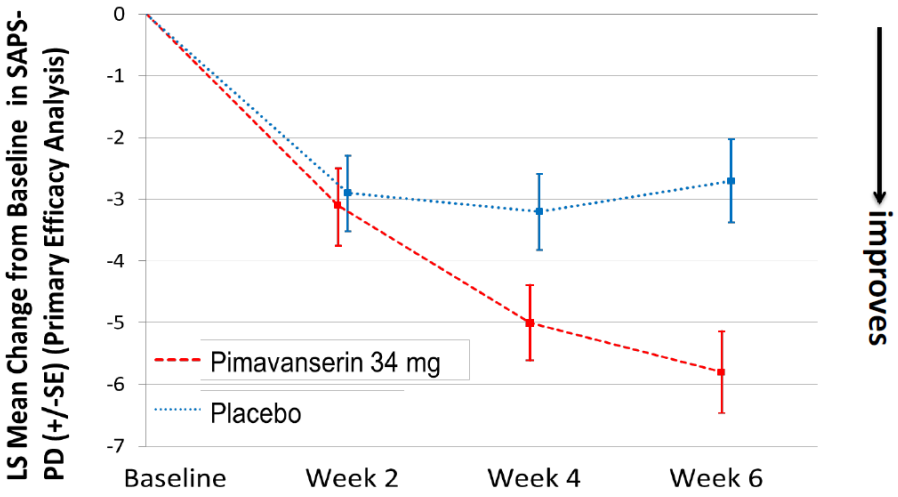
**Figure 2 Proportion of Patients with SAPS-PD Score Improvement at the End of Week 6 (N=185)**




It is clear that a fraction of treated patients has very substantial improvements. Note also that about 14% vs 1% have complete resolution of hallucinations and delusions.

The time course of effects on SAPS-PD is shown in Fig 3.

**Figure 3: SAPS-PD vs. Time (Study 020; N=185)**




Dr. Mathis shows a range of demographic subgroup analyses.

**Table 2: Subgroup Analysis Study 020**

| Observed (Raw) data Primary Endpoint (SAPS-PD) | | Mean Change from Baseline at Week 6 (SD) | | | | |
|---|---|---|---|---|---|---|
| | | Pimavanserin | #Subjects | Placebo | #Subjects | Total Number of Subjects at Week 6 |
| Primary Analysis Set mITT population (N=185) | | -6.3 (5.88) | 87 | -2.7 (7.03) | 86 | 173 |
| Gender | Male | -7.3 (5.54) | 56 | -3.0 (6.82) | 50 | 106 |
| | Female | -4.7 (6.20) | 31 | -2.2 (7.38) | 36 | 67 |
| Race | White | -6.0 (5.81) | 82 | -2.3 (6.83) | 81 | 163 |
| | Non-white | -11.4 (5.18) | 5 | -7.8 (9.04) | 5 | 10 |
| Age Group | < 65 years of age | -5.0 (4.60) | 10 | -5.4 (5.14) | 11 | 21 |
| | ≥ 65 and < 75 years of age | -6.5 (6.14) | 47 | -2.3 (6.77) | 47 | 94 |
| | > 75 years of age | -6.6 (5.96) | 30 | -5.4 (8.00) | 28 | 58 |

SD denotes standard deviation.
Source: Tables 14.2.3.14 - 14.2.3.16 of the CSR

These analyses show generally similar results on the SAPS-PD in men and women. There are too few black patients and patients < 65 years old to make any comparison. There is some suggestion of a smaller effect in patients over 75.

As noted, a major planned endpoint was the effect of pimavanserin on Parkinson's Disease motor function status (UPDRS II and III), designed as a non-inferiority analysis. Table 3 shows that patients in both the pimavanserin and placebo groups were improved at week 6, with little difference between them. There is clearly no worsening, although

like all non-inferiority studies, the results would be more certain if assay sensitivity were well-documented, in this case ideally by another anti-psychotic that did show worsening on UPDRS-II & III. Certainly one can conclude that pimavanserin showed no apparent worsening but I would not support a comparative statement here.

**Table 3: Primary Analysis Results of Second Endpoint: Parkinson's Disease Status (UPDRS II+III) Change from Baseline to Week 6**

| ANCOVA (OC) LSM Estimate (SE) | | Difference from Placebo in LSM Estimate (SE) | 95% Confidence Interval | P value |
|---|---|---|---|---|
| Pimavanserin [N=92] | Placebo [N=88] | | | |
| -1.40 (0.86) | -1.69 (0.88) | 0.29 (1.23) | (-2.14, 2.72) | 0.8140 |

Note: A negative change from baseline indicates an improvement. The analysis result is based on ANCOVA (OC) model with treatment group as a factor and baseline score as a covariate. OC denotes Observed Cases. SE denotes standard error. N denotes the number of patients who had a baseline score and the endpoint score at Week 6.
Source: Reviewer's analysis

IV. Safety

Dr. Mathis addresses Dr. Andreason's safety concerns in his review. It should be noted that he does not agree that effectiveness of pimavanserin is minimal, when properly analyzed, and I agree – the mean effect is not the whole story.

Analysis of deaths and SAEs is challenging. The 3 deaths on treatment (a fourth was 30 days after last dose) and 1 death on placebo, shown in Dr. Mathis's review, ____: myocardial infarction in a 61 year old male, septic shock and septicemia in 74 and 76 year old males on drug and cardiopulmonary arrest on placebo in an 85 year old male. It is very hard to reach a conclusion from such numbers (3 vs 1 can be a chance occurrence) that deaths should be attributed to pimavanserin, but it is appreciated that deaths associated with antipsychotics used in dementia are similarly variable.

Considering long-term study open-label deaths (Andreason p 91-93), almost all of the deaths were in patients over 70 and all seem plausibly related to underlying disease or to patient age, although admittedly, without a control group, there is no ability to assess whether the rate is increased over what would be anticipated.

In controlled trials there were more serious adverse events (SAEs) on pimavanserin 34 mg (16/202, 8%) than on placebo (8/231, 3.5%), a nominally significant difference, but again with no unifying pathology. These are listed in Dr. Mathis's review, p 14-15 and Dr. Andreason's review, p 97-8.

**Table 4 Listing of Subjects with Serious Adverse Events in the PDP Placebo-controlled 6- week Studies (Population PDP6: ACP-103-012, ACP-103-014, and ACP-103-020)**

| Unique-Subject ID | Age/ Sex | Adverse Event Preferred Term | Study Days | Last Dose Day | Action Taken | Severity | Causality | Study DC Reason |
|---|---|---|---|---|---|---|---|---|
| **Placebo** | | | | | | | | |
| 012-011-004 | 79/F | Anaemia | 31-35 | 44 | Interrupted | Moderate | Not related | No |
| | | Gastrointestinal ulcer haemorrhage | 31-35 | 44 | Interrupted | Moderate | Not related | No |
| 012-019-004 | 82/F | Bronchitis | 46-49 | 46 | Interrupted | Severe | Not related | No |
| 014-071-002 | 73/M | Mental status changes | 14-19 | 14 | DC | Moderate | Possibly | Yes |
| 014-160-003 | 78/M | Gastroenteritis | 36-44 | 28 | Interrupted | Mild | Not related | No |
| | | Delirium | 36-44 | 28 | DC | Moderate | Unlikely | Yes |
| 020-010-112 | 77/F | Decubitus ulcer | 40-Unk | 47 | No change | Moderate | Not related | No |
| 020-028-101 | 85/M | Arrhythmia | 13-Unk | 27 | DC | Severe | Unlikely | Yes |
| | | Cardio-respiratory arrest | 36-36 | 27 | No change | Severe | Unlikely | Fatal |
| | | Transient ischaemic attack | 13-13 | 27 | No change | Moderate | Unlikely | No |
| 020-038-103 | 73/M | Urinary tract infection | 22-33 | 23 | DC | Moderate | Not Related | Yes |
| 020-320-101 | 72/M | Spinal fracture | 47-52 | 57 | No change | Moderate | Not related | No |
| **Pimavanserin 8.5 mg** | | | | | | | | |
| 012-004-002 | 87/M | Dementia with Lewy bodies | 5-Unk | 3 | No change | Mild | Not related | No |
| | | Encephalopathy | 3-7 | 3 | DC | Moderate | Unlikely | Yes |
| 020-011-103 | 61/M | Myocardial infarction | 46-45 | 46 | DC | Severe | Unlikely | Fatal |
| 012-016-001 | 70/M | Syncope | 6-7 | 6 | DC | Moderate | Possibly | Yes |
| 012-028-002 | 72/M | Cellulitis | 32-36 | 4 | No change | Moderate | Not related | No |
| | | Sepsis | 32-34 | 4 | No change | Severe | Not related | No |
| 012-116-007 | 67/M | Inguinal hernia repair | 44-49 | 50 | Interrupted | Mild | Not related | No |
| 014-072-005 | 78/F | Fall | 41-64 | 28 | DC | Severe | Unlikely | Yes |
| | | Hip fracture | 41-64 | 28 | DC | Severe | Unlikely | Yes |
| 014-154-012 | 53/M | Psychotic disorder | 42-81 | 41 | No change | Severe | Unlikely | No |
| 014-169-001 | 53/F | Delusion | 27-42 | 16 | No change | Moderate | Not related | No |
| | | Delusion | 3-7 | 16 | DC | Moderate | Not related | Yes |
| **Pimavanserin 17 mg** | | | | | | | | |
| 014-068-003 | 68/M | Parkinson's disease | 11-7 | 11 | DC | Moderate | Not related | Yes |
| **Pimavanserin 34 mg** | | | | | | | | |
| 012-013-001 | 79/M | Mental status changes | 3-4 | 2 | DC | Severe | Possibly | Yes |
| 012-106-001 | 72/M | Headache | 51-58 | 36 | DC | Moderate | Possibly | Yes |
| 012-116-006 | 74/M | Confusional state | 9-9 | 8 | No change | Severe | Not related | No |
| | | Hallucination | 9-12 | 8 | DC | Severe | Not related | Yes |
| 012-117-002 | 77/F | Breast cancer | 36-36 | 32 | DC | Severe | Not related | Yes |
| 012-118-001 | 84/F | Syncope [a] | -28 to -21 | 29 | No change | Moderate | Not related | No |
| | | Respiratory distress | 32-61 | 29 | DC | Severe | Unlikely | Fatal |
| 020-001-101 | 76/M | Multi-organ failure | 10-Unk | 9 | No change | Severe | Not related | No |
| | | Septic shock | 10-10 | 9 | No change | Severe | Unlikely | Fatal |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Psychotic disorder | 4-Unk | 9 | DC | Severe | Not related | Yes |
| | | Sleep disorder | 4-Unk | 9 | No change | Severe | Not related | No |
| 020-011-103 | 82/M | Fall | 2-2 | 15 | No change | Moderate | Unlikely | No |
| | | Mental status changes | 2-6 | 15 | No change | Moderate | Unlikely | No |
| 020-013-102 | 69/M | Haemorrhoids | 36-39 | 40 | No change | Severe | Unlikely | No |
| 020-019-105 | 80/F | Bronchitis | 36-43 | 11 | No change | Severe | Not related | No |
| | | Septic shock[a] | 48-82 | 11 | No change | Severe | Not related | No |
| 020-019-106 | 72/F | Atrial fibrillation | 26-27 | 45 | No change | Moderate | Not related | No |
| 020-038-104 | 78/F | Urinary tract infection | 2-36 | 1 | DC | Mild | Not related | Yes |
| 020-039-103 | 74/M | Asthenia | 6-6 | 5 | DC | Severe | Unlikely | Yes |
| | | Fatigue | 6-6 | 5 | DC | Severe | Unlikely | Yes |
| | | Urinary tract infection | 6-12 | 5 | DC | Severe | Not related | Yes |
| | | Dehydration | 6-6 | 5 | DC | Severe | Unlikely | Yes |
| 020-063-110 | 80/F | Urinary tract infection | 12-15 | 43 | No change | Moderate | Not related | No |
| 020-303-121 | 74/M | Sepsis | 42-45 | 38 | No change | Severe | Not related | Fatal |
| | | Psychotic disorder | 38-Unk | 38 | DC | Severe | Possibly | Yes |
| 020-308-103 | 74/M | Parkinson's disease | 41-61 | 40 | No change | Severe | Unlikely | No |
| 020-327-105 | 79/M | Syncope[a] | -11 to -5 | 42 | No change | Moderate | Not related | No |
| 020-330-101 | 72/F | Hallucination | 16-Unk | 7 | No change | Severe | Not related | No |

Source: Listing PDP6 2-3.1 and ISS page 247

There are many oddities. Considering the placebo and 34 mg patients:
Many of the reported serious events on 34 mg do not seem to be SAEs (headache, hemorrhoids, urinary tract infection) and many others seem to be manifestations of the underlying disease (mental status changes, confusional state/hallucination, Parkinson's Disease, hallucination). Subtracting these we get, on pimavanserin 34 mg:

- breast cancer – obviously unrelated
- syncope/respiratory distress
- multi-organ failure/septic shock/psychiatric disorder/sleep disorder
- fall/mental status changes
- bronchitis/septic shock
- atrial fibrillation
- asthenia/fatigue/UTI
- sepsis/psychiatric disorder
- syncope

On placebo we get:

- anemia, GI ulcer, hemorrhage
- bronchitis
- gastroenteritis/delirium
- decubitus ulcer
- arrhythmia, cardio-respiratory arrest, TIA
- spinal fracture

This leaves 9 vs 6 (omitting the underlying disease and other psychiatric manifestations and what seem to be non-serious events. No doubt these could be debated, but they do not seem to me to represent an apparent effect of pimavanserin.



Reference ID: 3924880

V. Conclusion

The effect of pimavanserin in treating PDP is well-established by Study 020 with some support in 012. In Study 020 the primary endpoint shows an effect at a low p-value (0.0014) and there are effects on CGI as well, an entirely independent assessment. The effect is not minimal when the range of effects is considered. Pimavanserin does not worsen PD motor/function.

There is concern, more historical than in present data over possible serious adverse effects of antipsychotics in fragile individuals but the present data do not raise additional concerns. Pimavanserin should be approved for treatment of hallucinations and delusions associated with PD psychosis. Labeling will warn about increased mortality in patients with dementia-related psychosis treated with antipsychotic drugs, noting that pimavanserin is not approved for this use. The sponsor has committed to the conduct of a randomized withdrawal trial to establish continuing effectiveness, to further study of the 34 mg dose in frail elderly, not necessarily in PD (e.g., in Alzheimer's patients), to examining the effect of strong CYP3A4 inducers on pimavanserin exposure, and a further animal study to re-evaluate lung tissue samples to detect collagen in high dose treated animals.

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/s/

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ROBERT TEMPLE
04/29/2016